REMARKS

Reconsideration of this application, as amended, is respectfully requested.

At the outset, it is gratefully acknowledged that the Examiner has kindly allowed Claims 10, 19 and 34. It is further noted that the Examiner has objected to Claims 20 and 35, but only rejected Claim 22. Applicants believe that the present amendment will resolve the outstanding issues.

The Examiner made the restriction requirement final. Consequently, the compound and the process claims of this application have been limited to the elected invention to expedite prosecution towards an early allowance. Claim 1 has been rewritten to conform the generic compound claim to the allowable subject matter of Claims 10 and 19, plus a reasonable scope of substituents to the extent of the elected compound. Claim 20 has been amended to comprise the allowable species dependent upon the genus of Claims 10 and 19. Claim 35, which incorporated flowsheets by reference to the specification, has been canceled. New Claim 36 has been added to recite the process of making the allowable compounds of Claims 10 and 19. Support for Claim 36 is found in the description of Flowsheets 4-9 on pages 83-95 of the specification.

Despite the finality of the restriction requirement, Claims 23-33 have been retained with elected Claim 22 to afford the Examiner the opportunity to further evaluate the restriction of the method claims in light of the present response. First of all, the method claims were kept intact by the same Examiner in the parent application, issued under U.S. Patent No. 6,638,929, thus proving that the various diseases are interrelated and would not be expected to raise differing issues of patentability (see the attached true copy of Claims 5-15, cols. 167 and 168, of the '929 patent). There is absolutely no justification for treating the method claims differently in the present divisional application than in the parent case. Secondly, the biological activity recited in Claims 23-33 and described in the data of the working examples in the application refutes the enablement rejection of Claim 22. The showing of the broad-spectrum use of the compounds of the invention in a direct relationship with the various diseases supports the patentability of Claim 22. Thirdly, it appears from the Examiner's comments that he has in fact examined and found the subject matter of withdrawn Claims 23 (as it pertains to the neoplasm being colon and lung) and 31 (colonic polyps), in part or in full, allowable. Based on the foregoing rationale, Applicants respectfully ask the Examiner to maintain Claims 23-33 in the present application and consider their patentability in view of the current amendment.

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It is reiterated that Applicants reserve the right to file a divisional application directed to the remaining, nonelected subject matter of this claimed invention in due course.

Turning to the sole rejection at hand, the Examiner has rejected Claim 22 under 35 U.S.C. § 112, first paragraph, because, in his opinion, the specification, while being enabling for specific neoplasms (namely, colon cancer, lung cancer and colonic polyps), does not enable any person skilled in the art to use the invention commensurate in scope with this claim for reasons set forth on pages 3-7 of the Office action. Applicants respectfully traverse the rejection for the following reasons.

It is submitted that the invention disclosure would have enabled one of ordinary skill in the art at the time the application was filed to make and use the claimed invention without undue experimentation. Claim 22 is read in light of the specification, which teaches that the substituted aromatic tricyclic compounds containing nicotinonitrile rings of the present invention inhibit the action of protein kinases, thereby inhibiting the abnormal growth of certain cell types. The novel compounds are useful for the treatment or inhibition of diseases that are the result of deregulation of the protein kinases. As a consequence of the art-recognized correlation between deregulated protein kinase and uncontrolled cell proliferation, the compounds of this invention are expected to be anti-cancer agents and useful for the treatment, inhibition or eradication of cancer tumors in mammals (see the discussion in the Background of the Invention on pages 1-6 of the specification).

Furthermore, the factors of enablement support the Applicants' position as follows:

1) Nature of the invention: The nature of the invention involves novel tricyclic compounds containing nicotinonitrile rings and the unique use as inhibitors of the biological effects of deregulated protein tyrosine kinase. The treatment of neoplasms in Claim 22 is based on the demonstrated ability of the claim-recited compounds to directly inhibit several protein kinase pathways and cancer cell proliferation. The molecules and usage fall essentially in the same general class of patented compounds and methods of U.S. Patent No. 6,638,929.

2) State of the prior art: There is no art that precludes patenting the claimed method. The Examiner's reliance on the extrinsic evidence of Draetta *et al.* in "Annual Reports in Medicinal Chemistry" is misplaced. The specification has not taught that Claim 22 is intended to be a universal cure for all neoplasms. Although the claimed method includes eradication of

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neoplasms as one option, it also claims treatment and inhibition of the growth of neoplasms as two other alternative options. Because there is an art-recognized correlation between the standard assays relied upon by Applicants in the application and the use of the tricyclic compounds of the invention to treat, to inhibit the growth of and to eradicate a wide range of neoplasms, the state of the prior art supports making the claim.

3) Level of one of ordinary skill in the art: Chemotherapy has advanced to the extent that one of ordinary skill in the art is able to predict the antineoplastic use of representative compounds against target cancers based on the results of *in vitro* tests through routine efforts. As a general rule, the oncologist can predict, select and administer appropriate chemotherapy to a cancer patient and have a reasonable expectation of success despite the fact that certain neoplasms are virulent and difficult to treat. For the more virulent neoplasms, success is measured by significantly extending a cancer patient's life beyond the expected mortality rate from the cancer. In the intractable cases, even if treatment does not result in a total cure or eradication of the cancer, the oncologist can still anticipate that the claim-recited compounds will be able to inhibit the *in vivo* growth of cancer cells based on the *in vitro* results commensurate in scope with Claim 22.

4) Level of predictability in the art: The Examiner has stated that determining if any particular neoplasm would be treatable with Applicants' compounds would require clinical trials in each disease with each compound. With all due respect, it is believed that this predictability factor refers to the ability of the ordinary biochemist or oncologist to extrapolate the disclosed results to the claimed invention. The predictability factor determines whether the biochemist or oncologist would have reasonable doubt as to the accuracy of the extensive data in the specification. In this case, there is no doubt that the compounds of this invention possess significant activity as inhibitors of protein kinases and neoplasms based on the predictability of the results from the standard pharmacological tests described in the application. Patentability does not require a disclosure of every operable species, exemplification of each and every embodiment of the invention or clinical trials in each disease with each compound.

5) Amount of direction provided by the inventor: On pages 123-143 of the specification, Applicants provide sufficient guidance to the public to enable one to practice and use the claimed invention without undue effort. Typical formulations and dosages are described on pages 141-143

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of the application. The further determination of specific formulations, dosages or dosing schedules for each compound is well within the ordinary skill of the pharmaceutical industry through routine testing and dose titration.

6) Existence of working examples: Although there is no statutory requirement for working examples, Applicants exemplify the method of Claim 22 through a considerable number of standard pharmacological test procedures. The working examples of the *in vitro* tests show that the compounds of the invention inhibit numerous kinase pathways such as EGFR or erbB2 (Her2) on pages 124-126 (Claim 24); MAPK on pages 127-128 (Claim 25); RAF kinase on pages 136-140 (Claim 26); SRC kinase on pages 128-129 (Claim 27); Mek-Erk on pages 127-130 (Claim 28); and VEGF/KDR on pages 126-130 (Claim 29). In addition, the working examples illustrate biological activity against a wide range of carcinogenic cell lines such as HT-29 and Ca-CO2 (colorectal adenocarcinoma) on pages 132-134; MDA-MB-435 and SK-BR3 (breast carcinoma) on pages 134-136; A431 (epidermoid carcinoma) on pages 134-136; SW620 and LoVo (colon cancer) on pages 134-136 and 138-140, respectively; LnCAP (prostate cancer) on pages 138-140; and BxPC3 (pancreatic cancer) on pages 138-140. Based on the broad-spectrum activity shown in the standard pharmacological tests, it is demonstrated that the compounds can inhibit deregulated protein kinase pathways that are known to cause proliferative cell disease as well as directly inhibit cancerous cell lines. Hence, the working examples clearly support the use of the claim-recited compounds as antineoplastic agents.

7) Breadth of the claims: A similar breadth of related compounds and the same scope of diseases embraced by Claim 22 have been permitted in the parent application that issued as U.S. Patent No. 6,638,929. Since the specification and the data are the same in the divisional application as the prior application, there is no justification for finding that the scope of instant Claim 22 is not reasonable. Considering all the various deregulated protein kinase pathways that can be inhibited by the compounds of the invention, the biological data clearly support the breadth of the claim.

8) Quantity of experimentation needed to make or use the invention based on the content of the disclosure: The specification clearly enables the ordinary practitioner to be able to practice the claimed method without undue experimentation. It is well within the ordinary skill of the biochemical and pharmaceutical arts to be able to handle this level and type of chemistry.

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Proof is demonstrated by the grant of U.S. Patent No. 6,638,929. The practitioner can easily determine which compounds to select to treat, inhibit the growth of or eradicate a neoplasm based on routine testing in the standard pharmacological test procedures described in the specification. Such routine testing does not preclude patentability.

As a consequence of the foregoing evidence, it is clearly shown that the factors of enablement support the Applicants' position and the patentability of Claim 22. In view of the foregoing remarks, it is respectfully requested that the rejection of Claim 22 under 35 U.S.C. § 112, first paragraph, be withdrawn and the application be held allowable.

The Examiner is encouraged to contact the undersigned attorney to discuss any objectionable substituent or compound remaining in amended Claims 1 and 20.

Accordingly, favorable treatment is respectfully urged.

Respectfully submitted,

WYETH

Date: February 14, 2005

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FILING BY EXPRESS MAIL UNDER 37 C.F.R. § 1.10

This correspondence is being deposited with the U.S. Postal Service on February 14, 2005 to be delivered by the "Express Mail Post Office to Addressee" service under Mailing Label Number ER 586233811 US addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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sss) 4-(2-Chloro-4-fluoro-5-methoxyanilino)-7-methoxy-8-[2-(4-methyl-1-piperazinyl)ethoxy]benzo[g]quinoline-3-carbonitrile,

ttt) 4-(3-Chloro-4-fluoroanilino)-8-methoxy-7-[2-(4-morpholinyl)ethoxy]benzo[g]quinoline-3-carbonitrile,

uuu) 4-(3-Chloro-4-phenoxyphenylamino)-7-methoxy-8-(2-morpholin-4-yl-ethoxy)benzo[g]quinoline-3-carbonitrile,

vvv) 4-(3-Chloro-4-phenoxyphenylamino)-8-methoxy-7-(2-morpholin-4-yl-ethoxy)benzo[g]quinoline-3-carbonitrile,

www) 4-(2-Chloro-5-methoxy-4-methylphenylamino)-8-methoxy-7-(2-morpholin-4-yl-ethoxy)benzo[g]quinoline-3-carbonitrile,

xxx) 4-(2-Chloro-5-methoxy-4-methylphenylamino)-7-methoxy-8-(2-morpholin-4-yl-ethoxy)benzo[g]quinoline-3-carbonitrile,

yyy) 4-(4-Benzyloxy-3-chlorophenylamino)-8-methoxy-7-(2-morpholin-4-yl-ethoxy)benzo[g]quinoline-3-carbonitrile,

zzz) 4-(4-Benzyloxy-3-chlorophenylamino)-7-methoxy-8-(2-morpholin-4-yl-ethoxy)benzo[g]quinoline-3-carbonitrile,

aaaa) 8-(Benzyloxy)-4-[(2-chloro-4-fluoro-5-methoxyphenyl)amino-7]-7-methoxybenzo[g]quinoline-3-carbonitrile,

bbbb) 4-[(2-Chloro-4-fluoro-5-methoxypheny-1)amino]-8-hydroxy-7-methoxybenzo[g]quinoline-3-carbonitrile,

or a pharmaceutically acceptable salt thereof.

5. A method of treating, inhibiting the growth of, or eradicating a neoplasm in a mammal in need thereof which comprises providing to said mammal an effective amount of a compound as described in claim **1**.

6. The method according to claim **5** wherein the neoplasm is selected from the group consisting of breast, kidney, bladder, mouth, larnyx, esophagus, stomach, colon, ovary, lung, pancreas, liver, prostate, and skin.

7. The method according to claim **5** wherein the neoplasm expresses EGFR or erbB2 (Her2).

8. The method according to claim **5** wherein the neoplasm depends, at least in part, on the RAS to MAPK kinase pathway.

9. The method according to claim **5** wherein the neoplasm depends, at least in part, on the SRC kinase pathway.

10. The method according to claim **5** wherein the neoplasm depends, at least in part, on the ECK/LERK-1 pathway.

11. The method according to claim **5** wherein the neoplasm depends, at least in part, on the VEGF/KDR pathway.

12. A method of treating, inhibiting the progression of, or eradicating polycystic kidney disease in a mammal in need thereof which comprises providing to said mammal an effective amount of a compound described in claim **1**.

13. A method of treating, inhibiting, or eradicating colonic polyps in a mammal in need thereof which comprises providing to said mammal an effective amount of a compound described in claim **1**.

14. A method of inhibiting the biological effects of a deregulated protein kinase in a mammal which comprises providing to said mammal an effective amount of a compound described in claim **1**.

15. A method of treating a disease or inhibiting a disease state whose etiology is at least in part caused by a defect in a signaling pathway upstream from a protein kinase; by overexpression of a protein kinase; or by a dysregulated protein kinase in a mammal in need thereof which comprises providing to said mammal an effective amount of a compound described in claim **1**.

16. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound described in claim **1**.

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